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In the Office Action of October 30, 2002, the Examiner rejected Claims 106-142 under 35 U.S.C. § 112, first paragraph, for lack of enablement.

Applicants respectfully traverse these rejections and request that the Examiner consider the following remarks in response to the Office Action.

Claim 115 has been amended to clarify that the cells instilled into a patient are transformed cells. Support for this amendment may be found, for example, at page 16, lines 10-12 and at page 20, lines 12-14, of the specification.

**Claim Rejections:**

**35 U.S.C. § 112, First Paragraph**

The Examiner has rejected Claims 106-142 of this application as allegedly not being enabled.

The Examiner noted that Claims 106-108 would be considered allowable if the application provided an alternative use for the methods of introducing a protein in a mammal other than the treatment of a disease. Applicants thank the Examiner for this indication but direct the Examiner to consider that the utility of treating diseases is established for the entirety of the claimed subject matter.

Specifically, Applicants respectfully direct the Examiner's attention to the declaration of Elizabeth G. Nabel, M.D. (hereafter the "Nabel Declaration"), which demonstrates that expression of therapeutic levels of protein sufficient to treat a cardiovascular condition can be achieved in accordance with the claimed subject matter by following the guidance of the present application. More specifically, the Nabel Declaration demonstrates that porcine vascular smooth muscle cells

(VSMCs) transformed to express p27, and then instilled into the pig from which they originated, have the therapeutic effect of reducing intimal hyperplasia.

Therefore, Applicants submit that an alternative utility for the method of introducing a protein in a mammal, other than treatment of a disease, is not required under 35 U.S.C. § 112, first paragraph.

The Examiner also states that Claims 106-142 are not enabled because the specification fails to provide an enabling disclosure for the treatment of any condition or disease by the site-specific instillation of any type of autologous or syngeneic vascular cells, endothelial cells, smooth muscle cells, or parenchymal cells in any mammal.

Specifically the Examiner states that "while the specification is primarily directed to the administration of **transformed** endothelial cells to blood vessels *in vivo* for the treatment of cardiovascular conditions, the claims broadly read on the administration of **untransformed** vascular cells for the treatment of disease" (Office Action, p. 4). Applicants have amended the claims to clarify that the cells instilled in Claims 106-142 are **transformed** cells. Therefore, Applicants submit that they have overcome this aspect of the rejection and respectfully request that it be withdrawn.

The Examiner further states that the specification fails to provide evidence that the delivery of any type of transformed cell to any other cellular location using any method of delivery would result in the expression of therapeutic levels of protein or the treatment of any disease or condition. Applicants respectfully direct the Examiner's attention again to the Nabel Declaration, which demonstrates that by following the teaching and guidance of the present application, one of skill in the art would be able to use an adenovirus vector encoding the p27 protein to transform vascular smooth muscle cells (VSMCs) from a pig. The Nabel Declaration also demonstrates that when these transformed cells were instilled into a balloon-injured artery of the same pig, they

expressed sufficient p27 to inhibit intimal hyperplasia. Hence, the work described in the Nabel Declaration demonstrates that expression of therapeutic levels of protein sufficient to treat a cardiovascular condition can be achieved in accordance with the claimed subject matter by following the guidance of the present application.

Moreover, Applicants submit that those of ordinary skill in the art at the time of the invention, following the application as a template, could transform cells and deliver them to an animal or human in accordance with the presently claimed invention to treat a disease using a desired gene product for treating that disease.

First, the mechanics of selecting vectors, promoters and genes and combining them into expression constructs and transforming cells were well known at that time.

Second, the present specification describes several examples of gene products that might be used with the present invention to treat various diseases. For example, at page 10, lines 7-16, 22-26, page 27, lines 11-27, and page 28, lines 1-13, the present specification describes treating ischemic cardiomyopathy and peripheral vascular or cerebrovascular conditions by introducing angiogenic factors, such as tPA, urokinase, streptokinase, transforming growth factor  $\alpha$ , transforming growth factor  $\beta$ , angiogenin, tumor necrosis factor  $\alpha$ , tumor necrosis factor  $\beta$ , acidic fibroblast growth factor, and basic fibroblast growth factor, into the circulation. At these pages, the present specification also describes treating diabetes mellitus by introducing glucose-responsive insulin secreting cells, as well as using  $\alpha$ -antitrypsin inhibitor to treat the liver and/or hypercholesterolemia. In addition, at these pages, the present specification describes treating a malignancy using specific recombinant toxin genes, such as diphtheria toxin, pertussis toxin, and cholera toxin.

Therefore, in light of the disclosure of the present specification in combination with Applicant's having demonstrated transformation and cell delivery using a marker protein and a therapeutic protein, there is no evidence of record suggesting that the one skilled in the art would not be able to apply the presently claimed methods to treat other diseases.

Hence, the present specification and the state of the art enabled one of skill in the art to practice the invention with a reasonable expectation of success.

Therefore, Applicants submit that this ground of rejection has been overcome and respectfully request that it be withdrawn.

The Applicants respectfully assert that claims 106-142 are now in condition for allowance and respectfully request that a notice of allowance be issued in this case. Should the Examiner feel a discussion would expedite the prosecution of this application; the Examiner is kindly invited to contact the undersigned.

Respectfully Submitted,

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